REMARKS AND ARGUMENTS

A. The Rejections of Claims 44, 47, 48, 61 and 62 Under 35 U.S.C. § 103(a) Should Be Withdrawn

At page 4 of the Office Action, the Examiner rejected pending claims 44, 47, 48, 61 and 62 under 35 U.S.C. § 103(a) over Huse et al. Science 1989 (*Huse)* and U.S. Patent 5,427,908 to Dower et al. (*Dower).*

In application to claim 44, the Examiner characterized *Huse* as "teaching methods of producing, screening, and isolating Fab comprising providing a combinatorial library (i.e. *in vitro* mutagenized nucleic acid from an existing antibody coding sequence), producing lambda phage particles displaying Fab, contacting the Fab phage displayed library with antigen, and separation via nitrocellulose lifts." See pages 4-5 of the Office Action. Thus, the Examiner's rejection, at least in part, is based on the conclusion that the *Huse* reference discloses lambda phage particles displaying Fab. However, as explained in more detail below, *Huse* does not disclose a display at the surface of lambda phage or any phage for that matter.

Huse depicts its constructs and vectors in Figure 1. As can be seen from the Figure, the *Huse* constructs are standard lambda expression vectors for production of antibody fragments in bacterial colonies. As also can be seen from Figure 1, there is no fusion with **any coat protein** in the *Huse* constructs or co-expression of a coat protein. Because there is no fusion with a coat protein in the *Huse* constructs or co-expression with a coat protein, there is no display of the *Huse* recombinant proteins at the surface of a phage. Instead, the *Huse* recombinant proteins are expressed inside of infected cells and then released once lysis of the cell is triggered. *Huse* employs a standard nitrocellulose based plaque screening to identify those phage that express recombinant proteins of interest.

Specifically, column 2 on page 1280 of *Huse* describes plaque screening in which each and every clone is examined to determine if it expresses an antibody fragment of interest: see for example the reference to "the screening methods used have allowed one to survey the gene products of at least 50,000 clones per plate so that 10^6 to 10^7 antibodies can be readily examined

in a day but the most powerful screening methods depend on selection." Thus, *Huse* does not disclose displaying molecules at the surface of bacteriophage. Further, the *Huse* method operates in two steps: first, there is laborious screening to identify, one by one, a phage plaque that produces a protein of interest; and second, there is laborious cloning out of a DNA sequence for the protein of interest from the bacterial cells.

Applicants refer the Examiner to the following paragraph at page 6 of the instant specification which further explains the term "particles displaying a population of specific binding pair members," as recited by the pending claims.

> Surprisingly, the applicants have been able to construct a bacteriophage that expresses and displays at its surface a large biologically functional binding molecule (e.g. antibody fragments, and enzymes and receptors) and which remains intact and infectious. The applicants have called the structure which comprises a virus particle and a binding molecule displayed at the viral surface a 'package'. Where the binding molecule is an antibody, an antibody derivative or fragment, or a domain that is homologous to an immunoglobulin domain, the applicants call the package a phage antibody' (pAb).

Thus, unlike the *Huse* method, the present invention requires that specific binding members be displayed at the surface of a bacteriophage. In keeping with this notion, all pending claims recite a limitation to "filamentous bacteriophage particles displaying a population of specific binding pair members."

In conclusion, the "phage library" of *Huse* is a set of standard lambda phage expression vectors, with absolutely no display of any binding molecule at the surface of any particle as recited by the pending claims. Thus, *Huse* does not disclose or suggest a phage display of Fabs as recited by the pending claims.

At page 5 of the Office Action, the Examiner combined teachings of *Huse* with those of *Dower*. The Examiner characterized *Dower* as teaching filamentous bacteriophage and concluded that "the combination of the method taught by *Huse* with the filamentous bacteriophage taught by *Dower* would have been obvious because the substitution of one known

element (i.e. lambda phage) for another (i.e. filamentous phage) would have been conventional to one of ordinary skill in the art. In addition, the specific phage utilized would have been an experimental design choice based on the desired outcome, future manipulation/experiments, and/or resources available."

Applicants respectfully disagree with the Examiner and traverse the rejection because the Applicants submit that a person of ordinary skill in the art would not have seen Dower as providing an obvious substitute for the lambda phage system described by Huse. As described in more detail above, lambda phage express proteins in a fundamentally different way than that presently claimed. As described in Huse, they do not express antibodies fused to a coat protein, there is no co-expression of an antibody with a coat protein, antibodies are expressed in the cell and the lambda phage infected cells are lysed by the phage thereby releasing the antibody which is identified by screening plaques using standard nitrocellulose plaque lifts. Given these vast differences, the Applicants submit that one of ordinary skill in the art would not have seen Dower as providing an obvious substitute or experimental design choice and therefore the combination of the references cannot properly render the present invention obvious.

In view of the forgoing, the Applicants request withdrawal of the rejections under 35 USC 103(a) should be withdrawn.

CONCLUSION

Applicants believe that the instant application is now in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the (312) 595-1408.

Respectfully submitted,

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